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| KUBELIK, ANNE R | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1638 | |

DATE MAILED: 02/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/019,661 | ZHANG ET AL. | |
| | Examiner | Art Unit | |
| | Anne R. Kubelik | 1638 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3-5,7,9-13 and 19-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7,9-13 and 19-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 23 November 2005 has been entered.

2. Claims 1, 3-5, 7, 9-13 and 19-21 are pending.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Claim Rejections - 35 USC § 112*

4. Claims 1, 3-5, 7, 9-13 and 19-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is modified from the rejection set forth in the Office action mailed 24 May 2005. Applicant's arguments filed 26 September 2005 have been fully considered but they are not persuasive.

A full review of the specification indicates that nucleic acids encoding bacterial autoinducer inactivation proteins are essential to the operation of the claimed invention. As the protein and its activity are novel, then is no well-developed field of prior art.

The claims are drawn to a genus of bacterial autoinducer inactivation protein-encoding nucleic acids that hybridize to any nucleic acid that encodes SEQ ID NO:2 under hybridization conditions in which only the wash is described; thus, the claim is very broad.

The specification does not describe any structural characteristics of the claimed nucleic acids. The structural features that distinguish bacterial autoinducer inactivation protein-encoding nucleic acids that hybridize to any nucleic acid that encodes SEQ ID NO:2 from other nucleic acids that hybridize to any nucleic acid that encodes SEQ ID NO:2 are not described in the specification. The specification provides no description of how the structure of SEQ ID NO:2 relates to the structure of other bacterial autoinducer inactivation proteins. The specification describes no structure required for the recited function, and the necessary and sufficient structural elements of a protein with bacterial autoinducer inactivation proteins are not described.

The only species described in the specification is SEQ ID NO:1, which encodes SEQ ID NO:2. One of skill in the art would not recognize that Applicant was in possession of the necessary common attributes or features of the genus in view of the disclosed species. Thus, since the disclosure fails to describe the common attributes that identify members of the genus, and because the genus is highly variant, SEQ ID NO:1 alone is insufficient to describe the claimed genus.

Hence, Applicant has not, in fact, described nucleic acids that encode a bacterial autoinducer inactivation protein within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and functional characteristics of the claimed compositions, it is not clear that Applicant was in possession of the claimed genus at the time this application was filed.

Claims 19-21 are drawn to a method of isolating bacterial autoinducer inactivation protein-encoding nucleic acids that hybridize to any nucleic acid that encodes SEQ ID NO:2 wherein the method requires plant and soil samples that contain a bacterial autoinducer inactivation protein-encoding nucleic acid. The level of skill and knowledge in the art at the time of filing was such that such plant and soil samples were not known at the time of filing; even the isolate Applicant used to isolate SEQ ID NO:1, 240B1, is not publically available.

The specification describes no such plant and soil samples and does not describe the structural features that distinguish plant and soil samples that contain a bacterial autoinducer inactivation protein-encoding nucleic acid from plant and soil samples that do not contain a bacterial autoinducer inactivation protein-encoding nucleic acid. Thus, one of skill in the art would not recognize that Applicant was in possession of the necessary common attributes or features of the genus

Because the plant and soil samples are not described, the method of using the plant and soil samples is likewise not described, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and functional characteristics of the compositions used in the claimed methods, it is not clear that Applicant was in possession of the claimed genus at the time this application was filed.

Applicant urges that written description is satisfied and one of ordinary skill in the art would know they are in possession of the claimed invention (response pg 8).

This is not found persuasive because the necessary and sufficient structural features of nucleic acids that encode AiiA proteins are not described within the full scope of the claims.

The portion of the previous rejection about signal peptides is withdrawn.

Applicant urges that the donor organisms are described in the specification on pg 15, line 6 (response pg 9).

This is not found persuasive because pg 15, line 6 merely states that bacterial isolated from plant and soil samples were screened. This does not describe plant and soil samples that contain a bacterial autoinducer inactivation protein-encoding nucleic acid.

See *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (CA FC 2004) at page 1894:

> Rochester also attempts to distinguish Fiers, Lilly, and Enzo by suggesting that the holdings in those cases were limited to composition of matter claims, whereas the '850 patent is directed to a method. We agree with the district court that that is "a semantic distinction without a difference." Univ. of Rochester, 249 F. Supp. 2d at 228. Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods. As the district court observed, "[t]he claimed method depends upon finding a compound that selectively inhibits PGHS-2 activity. Without such a compound, it is impossible to practice the claimed method of treatment."

5. Claims 1, 3-5, 7, 9-13, and 19-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding SEQ ID NO:2, does not reasonably provide enablement for bacterial autoinducer inactivation protein-encoding nucleic acids that hybridize to any nucleic acid that encodes SEQ ID NO:2, vectors comprising them, cells transformed with the vector and a method of using the nucleic acids to increase disease resistance in a plant. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection is modified from the rejection set forth in the Office action mailed 24 May 2005. Applicant's arguments filed 26 September 2005 have been fully considered but they are not persuasive.

The claims are broadly drawn to bacterial autoinducer inactivation protein-encoding nucleic acids that hybridize to any nucleic acid that encodes SEQ ID NO:2, vectors comprising them, cells transformed with the vector and a method of using the nucleic acids to increase disease resistance in a plant.

The instant specification, however, only provides guidance for isolation of SEQ ID NO:1, which encodes SEQ ID NO:2, from bacterial isolate nonpublically available 240B1 (pg 12-17); and expression in *Erwinia carotovora* to produce a strain with decreased virulence on plants (pg 17-18).

The instant specification fails to provide guidance for bacterial autoinducer inactivation protein-encoding nucleic acids that hybridize to any nucleic acid that encodes SEQ ID NO:2, vectors comprising them, cells transformed with the vector and a method of using the nucleic acids to increase disease resistance in a plant.

The instant specification fails to provide guidance for which amino acids of SEQ ID NO:2 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain lactonase activity of the encoded protein. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional enzyme.

Making "conservative" substitutions (*e.g.*, substituting one polar amino acid for another, or one acidic one for another) does not produce predictable results. Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252) showed that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1). All these mutated proteins, however, would have at least 95% identity to the original protein. The nucleic acids encoding all these mutated proteins, however, would hybridize under high stringency to the nucleic acids encoding the original protein.

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate nucleic acids that hybridize to SEQ ID NO:1 or that hybridize to any nucleic acid that encodes SEQ ID NO:2. Making all possible single amino acid substitutions in an 250 amino acid long protein like that encoded by SEQ ID NO:1 would require making and analyzing $19^{250}$ nucleic acids. Because nucleic acids that hybridize to SEQ ID NO:1 or that hybridize to any nucleic acid that encodes SEQ ID NO:2 would encode proteins with many amino acid substitutions, many more than $19^{250}$ nucleic acids would need to be made and analyzed. Guo et al (2004, Proc. Natl. Acad. Sci. USA 101: 9205-9210) teach that while proteins are fairly tolerant to mutations

resulting in single amino acid changes, increasing the number of substitutions additively increases the probability that the protein will be inactivated (pg 9209, right column, paragraph 2). Thus, making and analyzing proteins with many amino acid substitutions that also have bacterial autoinducer inactivation activity would require undue experimentation.

Molina et al (2003, FEMS Microbiol. Ecol. 45:71-81) teach that application of lactonase-expressing bacterial strains eliminated the effectiveness of disease-suppressing bacteria, resulting in diseased plants (paragraph spanning the columns, pg 78). Zhang (2003, Trends Plant Sci. 8:238-244) teach that transformation of plants with another nucleic acid that encodes an enzyme that controls lactone levels resulted in disease resistant plants in one case, but more susceptible plants in the other, and suggest that these results mean fine-tuning is required to match host-pathogen combinations (paragraph spanning the columns, pg 242).

The specification does not teach under which promoters the nucleic acid that hybridizes to any nucleic acid that encodes SEQ ID NO:2 must be expressed from in plants to provide disease resistance.

As the specification does not describe the transformation of any plant with a nucleic acid that hybridizes to any nucleic acid that encodes SEQ ID NO:2, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those with increased disease resistance, if such plants are even obtainable.

The specification does not teach which organisms can be used as donor organisms in the method of claims 19-21. Additionally, as bacterial isolate 240B1 is not deposited or publicly available, it cannot even be used to isolate the nucleic acid of SEQ ID NO:1.

As the specification does not describe the isolation of a nucleic acid that hybridizes to any nucleic acid that encodes SEQ ID NO:2 from a publicly available donor organism, undue trial and error experimentation would be required to screen through the myriad of potential donor organisms encompassed by the claims to identify those that have a nucleic acid that hybridizes to SEQ ID NO:1 or that hybridizes to any nucleic acid that encodes SEQ ID NO:2, if such donor organisms are even obtainable.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

Applicant urges that hybridization is well-known, and the sequences for SEQ ID NO:1 and 2 are disclosed; the hybridization conditions mean that nucleic acids with 80% homology hybridize, citing a website. Applicant urges that acceptable evidence as to lack of enablement has not been provided (response pg 11-12).

This is not found persuasive. The specification does not teach bacterial isolates, other than the nonpublically available 240B1, from which bacterial autoinducer inactivation protein-encoding nucleic acids that encode SEQ ID NO:2 can be found; it also does not teach how to make such nucleic acids.

Furthermore, nucleic acids with 80% identity to the 750 nucleotides of SEQ ID NO:1 that encode SEQ ID NO:2 would have 150 nucleotide substitutions relative to those 750 nucleotides of SEQ ID NO:1. Thus, the claimed nucleic acids encompass those that encode proteins with 150 amino acid substitutions relative to the 250 amino acid SEQ ID NO:2; these proteins would

have 40% identity to SEQ ID NO:2. The specification does not teach how to make bacterial autoinducer inactivation proteins with 40% identity to SEQ ID NO:2.

Applicant urges that working examples of transformed plants are not required and plants to use are identified (response pg 12-13).

This is not found persuasive because Molina et al (2003, FEMS Microbiol. Ecol. 45:71-8 1) teach that application of lactonase-expressing bacterial strains eliminated the effectiveness of disease-suppressing bacteria, resulting in diseased plants (paragraph spanning the columns, pg 78). Zhang (2003, Trends Plant Sci.8:238-244) teach that transformation of plants with another nucleic acid that encodes an enzyme that controls lactone levels resulted in disease resistant plants in one case, but more susceptible plants in the other, and suggest that these results mean fine-tuning is required to match host-pathogen combinations (paragraph spanning the columns, pg 242). As the specification provides no working example of disease resistant plants produced by the claimed method, the unpredictability taught by the art is not overcome.

Applicant urges that the sequence for Bacillus sp. 240B1 is publically available, and pg 15 discloses bacterial isolates form plant and soil samples to use (response pg 14).

This is not found persuasive because the specification does not teach the sequence for the Bacillus 240B1 genome, nor does it teach how to assemble a bacterium from its genomic sequence. The only isolate disclosed on pg 15 is 240B1, and this isolate is not publically available. Thus, isolates that comprise nucleic acids that hybridize to nucleic acids that encode SEQ ID NO:2 are not taught in the specification.

6. Claims 1, 3-5 and 19-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections. The rejection is repeated for the reasons of record as set forth in the Office action mailed 24 May 2005. Applicant's arguments filed 26 September 2005 have been fully considered but they are not persuasive.

Claim 1 is indefinite in its recitation of "the coding portion of SEQ ID NO:1" in part (a). Any nucleic acid has at least 6 potential reading frames, and thus at least 6 coding portions. It is unclear to which the claim refers.

Applicant urges that Fig 4A teaches SEQ ID NO:1 and the specification teaches that the ATG starts at base 1 and the termination site is labeled by a thick underline (response pg 15).

This is not persuasive as no such underline is present in the figure. It is suggested that "the coding portion of" be replaced with the bases the encode SEQ ID NO:2.

## *Conclusion*

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

The central fax number for official correspondence is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Anne Kubelik, Ph.D.
February 9, 2006